DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE OF MENTAL HEALTH

National Advisory Mental Health Council

Minutes of the 206th Meeting

May 14, 2004

Minutes of the 206th Meeting of the National Advisory Mental Health Council

The National Advisory Mental Health Council (NAMHC) convened its 206th meeting in closed session for the purpose of reviewing grant applications at 10:30 a.m. on May 13, 2004, in the Neuroscience Center, Rockville, Maryland, and adjourned at approximately 5:00 p.m. (see Appendix A: Review of Applications). The NAMHC reconvened at the open policy session at 8:40 a.m. on May 14, 2004, in Building 31C, Conference Room 6, on the main campus of the National Institutes of Health, in Bethesda, Maryland. In accordance with Public Law 92-463, this policy meeting was open to the public until its adjournment at 1:00 p.m. Thomas R. Insel, M.D., Director, National Institute of Mental Health (NIMH), chaired the meeting.

Council Members Present at Closed and Open Sessions (see Appendix B for Council Roster)

Sergio A. Aguilar-Gaxiola, M.D., Ph.D. — Chairperson
Susan M. Essock, Ph.D.
Susan Folkman, Ph.D. — Thomas R. Insel, M.D.
Faye A. Gary, Ed.D., R.N.
Megan R. Gunnar, Ph.D. — Executive Secretary
Martha E. Hellander, J.D.
Renata J. Henry — Jane A. Steinberg, Ph.D.
Ned H. Kalin, M.D.
Jeffrey A. Lieberman, M.D.
James P. McNulty
Eric J. Nestler, M.D., Ph.D.
Charles F. Reynolds, III, M.D.
Peter Salovey, Ph.D.
Larry R. Squire, Ph.D.
Ming T. Tsuang, M.D., Ph.D.
Karen Dineen Wagner, M.D., Ph.D.
Stephen T. Warren, Ph.D.

Ex-Officio Council Members Present at Closed and/or Open Sessions

E. Cameron Ritchie, M.D., Department of Defense
Robert Freedman, M.D., Department of Veterans Affairs

Liaison Representative

Anne Matthews-Younes, Ph.D., Center for Mental Health Services, Substance Abuse and Mental Health Services Administration (SAMHSA)

Others Present at Open Policy Session

Janet Aker, *The Blue Sheet/Washington Fax*
Michelle Alonso, Anxiety Disorders Association of America
Virginia Anthony, American Academy of Child and Adolescent Psychiatry
Scott Barstow, American Counseling Association

Dan Blazer, American Association for Geriatric Psychiatry
Zola Boone, *The Link*
Jeff Brainard, *Chronicle of Higher Education*
Steve Breckler, American Psychological Association
Daniel Dolan
Jill Egeth, Federation of Behavioral, Psychological and Cognitive Services
Cynthia Folcarelli, National Mental Health Association
E. Aracelis Francis, Council on Social Work Education
Debra Franko, Academy for Eating Disorders
Blanca Fuertes, Health Research and Services Administration
Laura Lee Hall, National Alliance for the Mentally Ill
Maia Hurley, Alliance for Children & Families
Jocelyn Kaiser, *Science Magazine*
Alan Kraut, American Psychological Society
Alison Kutchma, Child and Adolescent Bipolar Foundation
David Kutchma, Child and Adolescent Bipolar Foundation
Alan Leshner, American Association for the Advancement of Science
Karen Melnyk, Society for Research in Child Development
Sherry Mills, ABT Associates
Pamela Moore, *Capitol Publications*
A. Noyes, *Research USA*
Neena Owusu-Ansah, Academy for Educational Development
William Northey, American Association for Marriage and Family Therapy
Brett Pelham, American Psychological Society
Bonnie Raombeen, National Institute of Child Health and Human Development
Stephanie Reed, American Association for Geriatric Psychiatry
Darrel Regier, American Psychiatric Association Research Institute
Tina Renneisen, Bazelon Center for Mental Health Law
William Sansalone, Georgetown University
James Scully, American Psychiatric Association
Angela Sharpe, Consortium of Social Science Associations
Viviana Simon, Society for Women's Health Research
Paul Sirovatka, American Psychiatric Association
Karen Studwell, American Psychological Association
Barb Wanchisen, Federation of Behavioral, Psychological and Cognitive Services
Thomas Webb, Summit County Juvenile Court
Karen White, Children and Adults with Attention Deficit Disorder
Elaine Young, University of Maryland Baltimore County
Joan Zlotnik, Institute for the Advancement of Social Work Research

OPEN POLICY SESSION: Call to Order/Opening Remarks

Thomas R. Insel, M.D., Director, NIMH, and Chairman, NAMHC, convened the open policy session of the 206th Council meeting at 8:40 a.m. on May 14, 2004, in Conference Room 6, Building 31C, on the campus of the National Institutes of Health (NIH), in Bethesda, Maryland. He extended a special welcome to Dr. Anne Matthews-Younes, who directs the Division of Prevention, Traumatic Stress, and Special Programs at the Center for Mental Health Services (CMHS), in the Substance Abuse and Mental Health Services Administration (SAMHSA). Dr. Matthews-Younes was in attendance for A. Kathryn Power, M.Ed., Director, CMHS, who is the liaison representative to Council but was unable to be at the session. Dr. Insel congratulated Council member Dr. Eric Nestler, the recipient of the 2004 Gill Center Award for his contributions to the field of neuroscience, and Dr. E. Cameron Ritchie on her forthcoming promotion to full Colonel.

Approval of the Minutes for the Previous Council Meeting

Following Dr. Insel's request for comments on the minutes of the February Council meeting and Dr. Aguilar-Gaxiola's noted correction to the minutes, a motion to approve the minutes was unanimously endorsed.

NIMH DIRECTOR'S REPORT

Drawing from his formal report (see http://www.nimh.nih.gov/council/dirreportMay04.pdf), Dr. Insel updated Council on the NIH-wide Roadmap activities (see http://nihroadmap.nih.gov). Noting that the Roadmap is progressing rapidly, Dr. Insel reported that more than 20 Requests for Applications (RFAs) have been issued, with others to follow in the near future. The latest RFA released by the NIH Roadmap invites applications for pilot programs to establish the Molecular Libraries Screening Centers Network (see http://grants1.nih.gov/grants/guide/rfa-files/RFA-RM-04-017.html). As a lead Institute on this activity, NIMH will be responsible for the review of the applications submitted in response to this RFA; NIMH also will be responsible for the review of applications received in response to the RFA on Interdisciplinary Health Research Training: Behavior, Environment and Biology (see http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-04-010.html). Dr. Insel noted that Dr. Mayada Akil is coordinating the Institute's activities in several Roadmap areas—Pathways to Discovery, Research Teams of the Future, and Re-engineering the Clinical Research Enterprise.

Another important NIH issue that has received extensive media attention is the conflict-of-interest accusations directed at senior NIH scientists that were first reported by the *Los Angeles Times* in December. Dr. Zerhouni responded to those allegations by assembling an internal review group and a Blue Ribbon Panel chaired by Dr. Bruce Alberts, President of the National Academy of Sciences, and Mr. Norman Augustine, Chairman of the Executive Committee, Lockheed Martin Corporation, to assess the status of conflict-of-interest policies and procedures and make recommendations for improvement. A May 6 Panel report (see http://www.nih.gov/about/ethics_COI_panelreport.htm) called for strict new rules regarding Institute directors' participation in outside activities and clarification of the process by which intramural scientists engage in extramural efforts and play a continuing role in the scientific

community. While the Panel recognized the importance of building public/private partnerships for health-related research, more transparent disclosures of outside activities were recommended. Dr. Zerhouni will attend another hearing on this issue in late May and continue to work with the Department of Health and Human Services regarding this important issue.

Dr. Insel recapped NIMH efforts to increase public awareness of the Institute's mission and activities. Over the past few years, the Institute has undertaken several initiatives, including a series of dialogue meetings in Alaska, Texas, Illinois, Pennsylvania, and the Four Corners region of the Southwest, one purpose of which was to solicit input on priority areas for research from constituents across the country. The Office of Constituency Relations and Public Liaison, led by Ms. Gemma Weiblinger, currently directs these activities, which includes the Outreach Partnership Program (OPP) (see http://www.nimh.nih.gov/outreach/partners/), under the leadership of Dr. Timothy Hays. This nationwide outreach partnership between NIMH and established partners in 50 States and the District of Columbia has as primary goals closing the gap between mental health research and clinical practice, informing the public about mental health disorders, reducing the stigma and discrimination associated with mental illness, and increasing the public's awareness of the importance of basic and clinical research in advancing knowledge of the brain and behavior. Recently, the National Institute on Drug Abuse (NIDA) formally joined the OPP to bring complementary information on substance abuse to the partners. Now OPP is working to increase collaboration with the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and SAMHSA to provide important information on alcohol abuse and alcoholism and mental health services.

The NIMH Web site also has been redesigned to be user-friendlier and target mental health issues of immediate and widespread public interest (see http://www.nimh.nih.gov). For example, the site now contains commentaries on the use of antidepressant medications for children (available at http://www.nimh.nih.gov/press/stmntantidepmeds.cfm). Dr. Insel acknowledged the work of Mss. Clarissa Wittenberg and Jean Baum and collaborating extramural scientists in this important activity.

In a similar vein, the NIMH public information print and radio campaign *Real Men, Real Depression* continues to make a stunning impact and receive numerous awards. Most recently, it was selected by the Marine Corps to be shown around the world on its closed circuit network and will be featured in the June issue of *Parade Magazine.*

Other notable NIMH activities include the tenth anniversary meeting of the Human Brain Project (see http://www.nimh.nih.gov/neuroinformatics/annmeeting.cfm). The meeting, which was organized by Dr. Steven Koslow and his staff, brought together interested individuals from diverse backgrounds, including astronomers, representatives from IBM, and other persons who work with large databases, to discuss recent discoveries and future plans for neuroinformatics.

Reflecting the importance of neuroinformatics for advancing our understanding of mental illness, Dr. Insel reported on the work of a group of investigators at the University of California, Los Angeles, including Drs. John Mazziotta and Arthur Toga. Their work points out the importance of developing detailed magnetic resonance imaging (MRI)-based atlases of both cortical and subcortical areas of the human brain rather than solely relying on neuroanatomic guides as done

in the past. These researchers found that there can be individual variation in brain structure over time. By scanning the brains of 3,000 people, they ascertained these individual variants as well as mapping *in vivo* imaging onto *ex vivo* imaging to examine chemical maps. Such a scrutiny of the visual cortex, for example, shows greater consistency at the level of neurochemical receptors than cortical maps derived from MRI studies. In addition, these investigators are using four-dimensional brain maps to demonstrate variance in the human brain as a function of age—i.e., changes in gray and white matter over time.

Dr. Insel presented a time-lapse video produced by a team of NIMH and University of California, Los Angeles scientists that compresses structural MRI scans of healthy children and teens over a 15-year period, from age 5 to 21 years, to show the loss of gray matter, mostly from posterior to anterior regions, as the brain matures and neural connections are pruned. Areas performing more basic functions—at the extreme back and front of the brain—apparently mature earlier, while areas for higher order functions are still changing at age 21. Although the frontal pole loses gray matter very quickly, the dorsolateral prefrontal cortex and parts of the superior temporal sulcus and gyrus are the last sections to mature. This finding is particularly relevant to researchers studying neuropathology since adolescence and young adulthood are the periods when many serious mental disorders, such as schizophrenia and bipolar disorder, typically emerge. More information on this work appears in the May 25, 2004, issue of the *Proceedings of the National Academy of Sciences*. *Time Magazine* also published in its May 10 issue, "Secrets of the Teen Brain" (see http://www.nimh.nih.gov/press/prbrainmaturing.cfm), a cover story showcasing the work of Dr. Jay Giedd and the NIMH Child Psychiatry Branch's longitudinal MRI study of brain development.

Dr. Insel next referenced a recent NIMH meeting to discuss cognitive perspectives on mental health practices—an outgrowth of the recommendations contained in the Council's report on translating basic behavioral and cognitive science into crucial diagnostic tests and mental health treatments (see http://www.nimh.nih.gov/publicat/nimhtranslating.pdf). The effort brought together experts from the services, basic behavioral, and cognitive arenas to address such questions as risk assessment and studying patients within a family context. The outcomes from that discussion are still evolving. Credit for organizing the meeting goes to NIMH staff members Drs. Howard Kurtzman and Junius Gonzales.

In conclusion, Dr. Insel reported that NIMH has joined with other NIH Institutes concerned with neuroscience to develop a detailed blueprint for coordinated research in this area—an activity initiated by Dr. Zerhouni last January in recognition of the many shared research opportunities among 14 Institutes and Centers that could leverage their limited budgets and common interests in understanding how the brain works in areas ranging from neurogenomics to behavior. Three general themes have emerged for the collaboration: neural development, neural degeneration, and neural plasticity. Another focus is on developing useful and shared tools and technologies—or defining the toolkit for the 21st century neuroscientist. The May 7 issue of *Nature Neuroscience* describes the initial efforts by six Institutes to lay out a vision for large-scale studies while simultaneously protecting smaller-scale projects with great potential (see Insel, T.R., Volkow, N.D., Landis, S.C., Li, T.-K., Battey, Jr., J.F., and Sieving, P. "Limits to Growth: Why Neuroscience Needs Large-Scale Science"). The investment in a Neuroscience Blueprint should help all researchers in this field advance our understanding of a variety of illnesses. One

notable accomplishment is the opening of Phase 1 of the John Edward Porter Neuroscience Center on the NIH campus in about 2 months. This will be the first NIH facility that is allocated to a particular theme where teams with collaborators across the NIH will work on important problems where a great deal of traction already exists.

Discussion

Answering a question from Dr. Freedman about the proposed occupants of the new Porter Neuroscience Center, Dr. Insel explained that, among others, NIMH staff members Dr. Heather Cameron, an expert on neurogenesis, Dr. Jacki Crawley, an expert in phenotyping, Dr. Husseini Manji, an expert in mood and anxiety disorders, and Dr. Kathleen Merikangas, an expert on genetic epidemiological research, will be joining the staff at the Center. Plans are underway for a second wave of moves when additional NIMH staff will join others at the Center.

In response to a query from Dr. Kalin about future directions and funding for the developing Blueprint, Dr. Insel elaborated that the goal is to have completed Blueprint plans by September.

Drs. Michael Huerta and Marlene Guzman from NIMH are coordinating much of the work along with Dr. Paul Scott from the National Institute of Neurological Disorders and Stroke (NINDS). With regard to funding, Dr. Insel noted that many Institutes already provide significant resources to the areas of research to be supported through the Blueprint. For example, NIMH is particularly interested in working on the Gene Expression Nervous System Atlas or GENSAT program that NINDS now leads. The Human Brain Project (HBP) is a good example of a cross-Institute initiative where relatively small contributions from many separate Institutes have yielded a substantial return in investment. The HBP is coordinated and sponsored by 15 Federal organizations across four Federal agencies: the National Institutes of Health [NIMH, NIDA, NINDS, National Institute on Deafness and Other Communication Disorders (NIDCD), National Institute on Aging (NIA), National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institute of Child Health and Human Development (NICHD), National Library of Medicine (NLM), National Cancer Institute (NCI), National Heart, Lung, and Blood Institute (NHLBI), NIAAA, National Institute of Dental and Craniofacial Research (NIDCR)], the National Science Foundation, the National Aeronautics and Space Administration, and the U.S. Department of Energy. Representatives from all of these organizations comprise the Federal Interagency Coordinating Committee on the HBP, which is coordinated by the NIMH. During the initial 10 years of this program, 241 investigators have been funded for a total of approximately $100 million.

PRIORITY SETTING FOR THE BASIC SCIENCES OF MENTAL HEALTH: FINAL REPORT

Dr. Alan Leshner, Chief Executive Officer, American Association for the Advancement of Science, and Executive Publisher of *Science Magazine*, said that in December 2003, the Council established the Workgroup on the Basic Sciences of Mental Health to review and recommend priorities for the Institute's existing extramural research portfolio in molecular, cellular, and behavioral neuroscience and basic behavioral and basic cognitive science. The context for convening this Workgroup was the anticipated deceleration of budget growth at NIMH in the coming years. Already large commitments to previously funded grants, he noted, limit the

discretionary budget for new initiatives. The Workgroup, composed of highly respected researchers and leaders in the field, was charged with considering the impact of the portfolio in terms of relevance to the mission of NIMH; the potential traction of areas of science (those that are ripe for making progress); and the innovative nature of the research areas in question. Council member Dr. Eric Nestler chaired the subgroup that focused on basic molecular and cellular neuroscience, and Dr. Richard Davidson, University of Wisconsin, Madison, chaired the subgroup on basic behavioral and behavioral neuroscience. Other participating Council members included Drs. Megan Gunnar, Peter Salovey, and Larry Squire and Mr. James McNulty. The support provided to the Workgroup by NIMH staff was exceptionally helpful and thorough, Dr. Leshner said.

The Workgroup's final report, "Setting Priorities for Basic Brain and Behavioral Science Research at NIMH" (available at http://www.nimh.nih.gov/council/bbbsresearch.pdf), presents two core conclusions: (1) both basic behavioral science and basic neuroscience are critical to achieving the NIMH mission and must be continued and (2) the current NIMH basic science portfolio is strong and serves the Institute's mission well, although there is room for improvement and modifications.

In conducting its review, the group identified several overarching principles that guided its work: (1) basic brain and behavioral research at NIMH should support its public health mission and primarily be directed toward understanding the potential causes, treatment, and prevention of mental illness and behavioral disorders; (2) high priority should be given to basic research that integrates or translates across multiple levels of analysis—from genetic, to molecular, to cellular, to systems, to complex overt behaviors; (3) research and training that is interdisciplinary in nature should be emphasized more in the basic science portfolio; and (4) more effort should be directed at examining the effects of environments on behavior at both the molecular and integrative systems levels, requiring the development of tools that will allow for intensive study in this area.

In applying these principles to the portfolio evaluation, the Workgroup identified several crosscutting themes that pertain to many aspects and topical areas within the portfolio and should be given high priority. For example, sex and gender differences need to be better understood with respect to the underlying mechanisms that modulate differential vulnerability to particular mental disorders. In addition, a better understanding of individual differences in basic behavioral and neural processes is one key to ascertaining vulnerability to psychopathology. Similarly, adolescence and earlier developmental phases are important periods in which the expression of certain psychiatric disorders increases and environmental influences on brain function become more apparent, yet little is known about the neural, physiological, and behavioral changes that underlie these developmental shirts and vulnerabilities. Another important issue is the development of more appropriate animal models for specific aspects of mental disorders. More attention also is needed to better understand the performance of animals in natural/naturalistic settings in order to study natural variation among individuals.

The Workgroup identified six areas for increased research emphasis that present great opportunities and represent critical areas for understanding mental illnesses:

1. Emotion—including the neurobiology of emotion, mood, and motivation as well as the interaction of emotion and cognition.
2. Development—especially brain changes that occur during periods of rapid neurobiological development in humans that are the critical for emerging mental illnesses; how neural activity and gene-environment interactions regulate late prenatal development; and the intersection of social and cognitive functioning with neurobiological development.
3. Social interactions—including the integration of social processes and behaviors with brain functioning and brain organization in both human and non-human species.
4. Neural circuitry research and mapping—that uses new cellular imaging tools; examines the interaction of psychotropic drugs and complex behaviors; focuses on synaptic mechanisms; applies molecular and genetic approaches to tracing complex neural circuits; and focuses on neuronal replacement.
5. Sex and gender differences and mechanisms—that impact the expression and treatment of mental illnesses.
6. Intracellular signal integration—within molecular and cellular domains that explains how multiple signal transduction pathways interact to produce integrated cellular responses.

The Workgroup also recognized that the development and adaptation of research tools and techniques would serve as catalysts for advancing the basic science of mental disorders and described five focus areas: appropriate animal models, ligand development, relevant computational models and modeling systems, standardization of behavioral tools, and neuroimaging tools.

The Workgroup devoted significant attention to designating research areas that although productive and important, would now benefit from a shift in focus:

1. Aspects of learning and memory—shifting focus to emphasize integration across levels of analysis (e.g., behavioral and neurobiological) and across domains within the behavioral cognitive area (e.g., how cognition is integrated across types of memory).
2. Sleep studies—moving beyond phenotyping sleep problems that occur in psychiatric disorders to more mechanistic studies of sleep in relation to waking behaviors to understand the molecular neurobiology and circuitry of sleep, arousal, attentional states, and sleep's influence on cognitive and affective processes.
3. Circadian biology—shifting from single focus studies of molecular, behavioral, or sensory level phenomena to an emphasis on more complex behaviors and brain functions that might be affected by circadian rhythms.
4. Stress—shifting the emphasis from acute to chronic stress, comparing different types of stress in terms of behavioral and biological consequences, and gaining a better understanding of resilience to stress as potential protective factors for mental disorders.
5. Neurotransmitter-signaling systems—moving from already extensively studied ones to understanding some of the less well researched signaling systems and how various systems are integrated and mediate aspects of neural circuitry.
6. Prejudice and stereotyping—encouraging more transparent relevance to mental illness and mental health (e.g., the effects of prejudice and discrimination as chronic stressors).

The Workgroup identified some research areas with both high scientific merit and public health relevance that might be better undertaken by other NIH Institutes, including: (1) visual and other primary sensory perception and motor processes—when studied as purely sensory phenomena and not in terms of mental illness; (2) metabolic/thermoregulation; and (3) characterization of normal development and aging processes that do not have compelling relevance to mental and behavioral disorders.

Finally, the Workgroup recognized that NIMH has a key leadership role in advancing the field. The group suggested that NIMH staff members continue to scrutinize the Institute's portfolio to identify research areas that are becoming overly subscribed and support only those applications offering the most innovative approaches. In addition, it may be useful for staff to work with the Center for Scientific Review (CSR) to ensure that initial review group membership reflects a stronger translational emphasis and multidisciplinary perspectives. NIMH also must create ways to foster and support translational research and research training by encouraging relevant grant applications and by fostering the development of training programs for basic scientists that encourage mental illness-relevant research.

In conclusion, Dr. Leshner noted that the Workgroup's report, while suggesting substantial changes, recognizes that the NIMH basic behavioral and neuroscience portfolio is in superb shape and serves the Institute's mission well. However, it would benefit from continued scrutiny and shifts in areas of emphasis. In doing so, the portfolio will be enhanced in terms of relevance, traction, and innovation for reducing the burden of mental illness.

Comments and Discussion

Dr. Nestler remarked that members of the Workgroup's molecular and cellular subgroup unanimously endorsed the importance of continuing basic neuroscience research at NIMH and conducting scientific experiments that are not directly related to a current disease state.

Dr. Salovey, elaborating on the meaning of "translational" research, recalled that NIMH has historically been committed to two streams of research: (1) basic science that emphasizes fundamental processes in neuroscience, cognition, emotion, and social behavior and (2) studies of psychopathologies and interventions to ameliorate them. Unfortunately, any connection between the two streams has often been lacking. Translational research, he continued, is intended to connect these two research streams by examining neurobiological, psychological, and social processes to determine how they are altered in mental illnesses and how they are affected by treatments.

Dr. Squire, speaking as a member of the behavioral neuroscience research subgroup, said that subgroup members strongly supported wide ranging behavioral and basic neuroscience research at the systems level, and research on brain systems that support emotion and attention, language, planning, executive function, and memory, as well as basic behavioral research that carefully describes phenomena and develops the tools for analysis needed to understand them. The Workgroup emphatically endorsed the basic research mission of NIMH—at the molecular, cellular, systems, and behavioral levels–and found the current basic science portfolio to be extraordinarily strong but that budget limitations require both quantitative and qualitative shifts.

Dr. Lieberman remarked that the challenge to Council will be to implement the Workgroup's recommendations. Dr. Leshner replied that the report contains specific, clear recommendations that can be executed. Nonetheless, NIMH should enlist various scientific societies and advocacy groups in the implementation plans.

Mr. McNulty noted a lack of understanding between some Workgroup members who are basic scientists and those in clinical areas and that a general consensus developed on the need for closer connections between the two perspectives. Much needs to be done, he said, to strengthen linkages between basic neuroscience and clinical practice.

Dr. Gunnar, expanding on Dr. Lieberman's comment about implementation, asked how Council could be certain that grant applications proposing work that is not relevant to the Institute's mission are deflected to another Institute prior to assignment to NIMH. Dr. Insel replied that NIMH will be modifying its referral guidelines that are used by CSR when assigning grant applications. During the interim, if, for example, the Workgroup recommends against supporting research on a specific topic and the Council endorses this decision, pending applications with good priority scores in this area may not be funded or staff may work to transfer such applications to another Institute for funding. It will be critical that the message on priorities be translated to the field.

When Dr. Tsuang asked how NIMH's relationship with CSR might be strengthened, Dr. Insel explained that CSR's role is to provide expertise that focuses on particular areas of science across many Institutes by soliciting the best reviewers to offer guidance about an application's scientific merit in a specified domain. It is Council's responsibility to determine whether applications with fundable priority scores or percentiles are aligned with the NIMH mission. Hence, in order to meet high program priority areas, Council has the authority to recommend that applications be designated high or low priority, which could impact the likelihood of funding an application.

Dr. Tsuang, expounding on the composition of CSR review committees, reflected that they are excellent training grounds for young investigators but may not attract sufficient senior scientists given the typical lengthy time commitment required for serving on review panels. He suggested it may be possible to recruit more senior scientists if the commitment was shortened to 1 or 2 years. Dr. Insel agreed that it is difficult to recruit reviewers and that more than 28,000 reviewers participated on review panels to consider about 66,000 applications this year.

In response to a query from Dr. Wagner regarding a balance in the basic science portfolio between human studies of children and adults and the need to study young children, Dr. Leshner explained that serious attention was given to the need for more studies of adolescents because this is the onset age for many mental illnesses, and recent research underscores the importance of brain changes that occur during that age period.

Ms. Hellander proposed to expand language in the report to address research on childhood and earlier developmental phases as young as birth, including prevention, the use of juvenile animal models, and genetic as well as environmental influences on brain development. Dr. Leshner

replied that Ms. Hellander's points were important, and Dr. Nestler added that developmental issues are one of the crosscutting themes highlighted in the report. Dr. Gunnar pointed out that gene-environment interactions during rapid periods of brain development also were emphasized as an area for increased research.

Dr. Gary asked whether the Workgroup had considered the implications the report might have for training and educating future scientists because some major restructuring will be needed in academia and clinical practice for all health professionals as well as epidemiologists, anthropologists, and sociologists to establish an interdisciplinary perspective that benefits from the wisdom of different disciplines in achieving the outcomes envisioned. Dr. Leshner replied that the report emphasizes interdisciplinary and translational approaches, with an explicit recommendation to integrate more training about clinical phenomena into basic science training and the reverse. While the report has significant implications for training, more resources will be necessary to accomplish these goals.

Dr. Insel invited Dr. Alan Kraut, Executive Director of the American Psychiatric Society, to comment on the report before Council voted on the report. Dr. Kraut remarked that three psychological scientists who were recently elected to the prestigious National Academy of Sciences—Drs. Elizabeth Loftus, Elisa Newport, and Walter Mischel—had each received critical NIMH support during their careers, which contributed to their success. Dr. Loftus' research reveals the malleability of memory and underscores the importance of understanding normal learning and memory as a basis for comprehending the abnormal cognitive functioning that accompanies much serious mental illness. Dr. Newport's basic linguistic research aims at understanding language and the cognition surrounding it as well as the special neural machinery undergirding it. Her findings, which demonstrate the remarkable human ability to acquire and maintain complex communication systems, are critical to understanding important aspects of such damaging illnesses as schizophrenia, autism, and aphasia. Dr. Mischel's work focuses on those characteristics of personality and emotion that change behavior in certain situations and are fundamental to understanding and treating a variety of mental disorders.

Although NIMH is proud of these grantees and their accomplishments, Dr. Kraut continued, the same three areas of basic research—learning and memory, linguistics, and personality–have been criticized externally and internally as irrelevant to clinical practice. He noted that this might be an appropriate time for NIMH to use the Workgroup's recommendations to reaffirm its commitment to the basic science of mental illness and to take advantage of the considerable science expertise already available at the Institute. It also may be an opportune moment to fill vacant NIMH positions with qualified researchers who appreciate basic behavioral science as well as the links between basic science and mental disorders. If NIMH is shouldering too much of the basic science burden in this time of diminished budgets, it should make certain that other NIH Institutes share the load. NIMH also should take a stand on where such important basic research belongs—at a reorganized NIMH and elsewhere at NIH. The promise of this type of research for advancing an understanding of mental disorders, as well as the long history of NIMH, demands it.

Acceptance of the Report

Before asking whether Council members concurred with the report, Dr. Insel noted that future Council meetings will include an opportunity to discuss ways to act on the report's recommendations. Dr. Insel called for a motion to accept the report, which was duly made, seconded, and unanimously supported by voice vote.

Dr. Insel thanked all members of the Workgroup for their hard work and extended credit to several NIMH staff members who provided stellar assistance, including Drs. Della Hann, Steve Foote, Linda Brady, Kevin Quinn, and Molly Oliveri.

NIMH OFFICE OF GLOBAL MENTAL HEALTH

Dr. Karen Babich, Director of the new NIMH Office of Global Mental Health, said that the Office was created in January 2004 to initiate and coordinate research efforts in addressing the global pandemic of mental illness. Three reports in the last decade document the immense and worldwide burden caused by the chronic nature of neuropsychiatric disorders: "The Global Burden of Disease" (see http://www.hup.harvard.edu/catalog/MURGLO.html), which describes depression as the fourth leading cause of disease burden in 1990 and likely the single leading cause by 2020; "The World Health Report 2001. Mental Illness: New Understanding, New Hope" (available at http://www.who.int/whr2001/2001/); and "Atlas: Country Profiles on Mental Health Resources 2001" (available at http://www.who.int/mental_health/media/en/243.pdf). She acknowledged the consultation provided by former Council members Drs. Javier Escobar and Norwood Knight-Richardson in crafting the Office.

The goals of the Office are: (1) to seek opportunities for global clinical research that will increase an understanding of both shared and culturally unique attributes of mental disorders, providers, and/or delivery systems; (2) to enhance the capacity of U.S. and international researchers to conduct global mental disorder-related research and to develop partnerships that can leverage resources; and (3) to work with international organizations and national institutes of mental health in other countries on shared goals and the exchange of resources (e.g., neuroinformatics and the burden of disease studies).

International research at NIMH is funded by three major mechanisms: (1) direct awards to foreign institutes for researcher-initiated research; (2) domestic awards with an international component (e.g., an award that is locally housed in a university but subcontracts with an investigator in a foreign institute where the research is conducted); and (3) Fogarty International Training and Research Programs. In 2003, the Office's international portfolio contained 192 of the approximately 3,600 grants awarded at NIMH. Of those, 29 were to foreign institutes and 163 awards were to domestic organizations with an international component. The Institute's $1.3 billion research budget for fiscal year 2003 included $20 million in support for international research of which 29 percent supported AIDS-related studies; 21 percent pertained to trauma, risk assessment, and other kinds of behavioral and cultural studies; 45 percent related to neuroscience—mostly epigenetic and genetic studies and training; and the remaining amount in treatment and services research grants. Most global research supported by NIMH is conducted

in Europe, including Russia, and focuses on a range of topics from neuroscience to AIDS research. There are at present no studies in the Eastern Mediterranean area, a situation expected to change in the future.

In addition to research, the Office is involved in other initiatives and collaborations with organizations, mainly within the Department of Health and Human Services, where the major partner is CMHS. The Office also works with the Fogarty Institute and with NIDA and NIAAA, particularly on comorbidity issues. Other organizations the Office collaborates with are the World Health Organization, the Pan American Health Organization, the Carter Center, the World Federation of Mental Health, the World Bank, the International Brain Research Organization, the Association for Women's Mental Health, and the Indian National Brain Research Center.

Discussion

Dr. Aguilar-Gaxiola expressed his enthusiasm for the new Office and thanked Dr. Escobar and others who were involved in its creation. Because the United States is, to a large extent, a nation of immigrants–and the world is becoming a global society—a lot of relevant information can be learned from other countries and from exchanges with them.

Dr. Ritchie added her appreciation and noted that the recent joint symposium by the American Psychiatric Association (APA) and the World Psychiatric Association, organized by Dr. Regier of APA, was not only a first but also offered an initial examination of mental health issues in Iraq. That work is continuing with the expectation that the Department of Defense will partner with NIMH, SAMHSA, and other organizations to develop this arena.

Ms. Hellander commended the initiative and added that the Child and Adolescent Bipolar Foundation (CABF) has a Web site that has received queries from over 100 countries and is building an online international database. CABF gets numerous e-mail requests for referrals from people in countries where there are no child psychiatrists. She encouraged the Office of Global Mental Health to establish Internet connections with developing countries, especially where isolated women have little access to information.

Mr. McNulty suggested that more international studies should focus on cultures in this hemisphere, especially Latin America, to reflect the changing demographics in the United States. He suggested that it would be timely to study how schizophrenia is experienced across the world and to negate any myth that living with this disorder in an undeveloped country is a benign experience.

CLINICAL TRIALS WORKGROUP: FINAL REPORT

Dr. Jeffrey Lieberman, Professor and Vice Chairman of the Department of Psychiatry at the University of North Carolina and Chairman of Council's Clinical Trials Workgroup, summarized the Workgroup's final recommendations. He began by noting that the charge to the Workgroup was to:

1. Review the portfolio of clinical treatment trials currently funded by the NIMH Division

of Services Intervention Research (DSIR) in light of scientific opportunities.
2. Assess the balance and relevance of the portfolio to the Nation's public mental health needs and burden of mental illnesses.
3. Identify any critical gaps in knowledge and scientific opportunities.
4. Assess the progress being achieved by currently funded grants and contracts.
5. Provide guidance regarding staff oversight for clinical trial performance sites.
6. Make recommendations for addressing any gaps or deficiencies.
7. Inform the development and implementation of future treatment research initiatives.

As background, Dr. Lieberman said that funding for clinical treatment trials is currently provided through a variety of mechanisms—research project grants (R01s), collaborative R01s, cooperative agreements, contracts, and centers. He noted that in Fiscal Year (FY) 2003, the largest proportion of funding for treatment trials supported studies of depression, followed by studies of schizophrenia, anxiety disorder, and bipolar disorder. Other areas included dementia, autism, attention deficit hyperactivity disorder, conduct disorder, and 21 "other" areas, including personality, eating, sleep, gambling, somatization, and traumatic grief disorders.

Regarding the distribution of funding by age group, the Workgroup found that the largest percentage of funding supported research on adults between the ages of 21 and 55 years, followed by studies of children and geriatric populations.

An examination of the race/ethnic status of adult subjects enrolled in DSIR-supported treatment trials that were completed and funded through a grant mechanism revealed that a majority of study subjects were Caucasian, followed by African American, Hispanic, and subjects who identified themselves as Asian, Hawaiian/Pacific Islander, American Indian/Alaskan, or "other." By comparison, the large-scale contracted Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trials included fewer Caucasian and more African American and Hispanic subjects.

The Workgroup also examined the success of investigator-initiated grants in meeting their subject recruitment goals: a significant number of projects studying children, adults, and geriatric subjects did not meet recruitment goals. This recruitment problem was also evidenced in minority populations. The implication of this finding is that steps need to be taken immediately to ensure that investigator-initiated clinical treatment trials funded through a grant mechanism are successfully conducted.

Since the capability to conduct effective treatment research also depends on building an adequate infrastructure of appropriately trained and dedicated investigators, the Workgroup examined the career development opportunities (K awards) that NIMH supports and found that during FY 2003, support for training for treatment-oriented research was limited.

After its thorough portfolio review, the Workgroup agreed on a number of evaluative statements. In general, the content areas of the DSIR research portfolio are of good quality and reflect a balance and proportional diversity in the range of disorders and age-relevant populations evaluating various somatic, pharmacologic, and psychosocial modalities that are currently or potentially indicated for treatment of mental disorders and behavioral disturbances. However,

the portfolio would be enhanced with greater breadth and depth across some major disorders (including bipolar disorder and anorexia); the portfolio related to particular areas of public mental health care (including polypharmacy, comorbidity, and treatment adherence) requires significant bolstering; and the portfolio in other areas appears to be somewhat over studied (e.g., ECT) or of decreasing relevance (e.g., tardive dyskinesia—in light of the effectiveness of atypical antipsychotic drugs without these side effects). The portfolio would be enhanced with more studies that include medical and psychiatric comorbidities, combination pharmacotherapies, and combined psychosocial/psychopharmacological treatments, which are the norm in clinical practice. Future studies must be designed to address the most compelling clinical and public mental health questions.

Dr. Lieberman highlighted several exceptional grants and contracts that have been awarded in recent years, noting that the trend toward excellent research is gaining momentum under Dr. Insel's leadership with the participation of Drs. Wayne Fenton, Grayson Norquist, and others. Several of the praiseworthy large contracts targeted on developing treatments for the cognitive deficits of schizophrenia are completing phase I efforts [e.g., the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and the Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) projects]. Also commendable, he said, are the treatment development initiatives that Dr. Linda Brady is leading in the Division of Neuroscience and Basic Behavioral Science. The NIMH approach, he said, is built on the assumption that progress in developing new treatments will require collaboration between the best academic, government, and industry scientists. Real progress will require significant changes in the way in which academic investigators conceive and conduct treatment-related research, an expansion in the number of clinical targets that ultimately will lead to the development of more novel compounds, improvements in the process by which members of review committees become oriented on NIH priorities and programs, and more involvement of constituents and stakeholders in establishing research priorities.

To strengthen the value of the treatment portfolio in meeting public mental health care needs and benefiting patients with serious mental illness, the Workgroup recommended that NIMH: (1) become more proactive in setting research priorities and demonstrating leadership; (2) recognize that treatment intervention research is inherently different from other forms of research in terms of the scope and costs of logistically complex, multisite, clinical trials, which are required to answer key questions about mental health treatment efficacy and effectiveness; (3) determine the proportional emphasis to place on various components of treatment development and effectiveness evaluations that comprise a continuum, beginning with the identification of cytomolecular targets or genes and continuing through the identification of new molecular entities and their synthesization and validation, testing in animal models and humans, effectiveness evaluations for populations of interest, and potential utility and cost effectiveness when delivered at a large-scale public mental health level; (4) monitor the performance of funded projects and provide needed guidance to ensure that study enrollment targets are met and goals achieved; and (5) maximize efficiencies in the conduct of intervention research by creating core resources, standard procedures, and enduring infrastructures that are available to extramural researchers who receive NIMH funding.

The Workgroup proposed a series of recommendations for NIMH activities that fall into three

broad categories:

Creating the Optimal Treatment Research Portfolio

- Establish a process that systematically seeks input from stakeholders in order to inform the future direction of treatment research and integrate public health interests with scientific opportunities
- Foster the development of innovative psychosocial, psychopharmacological, and somatic treatments
- Expand efforts to fund treatment research that optimizes existing treatments and facilitates their investigation in a range of healthcare settings

Building Clinical Trials Capacity and Expertise

- Develop and maintain large networks of sites reflecting community populations and relevant healthcare systems to answer important public health questions when investigator-initiated grants or efforts by the pharmaceutical industry are not likely to produce studies of sufficient size and scope to address these questions and provide confident answers
- Expand efforts to recruit and retain historically underrepresented subject populations, including ethnic and racial minorities and women, and underrepresented disorders in clinical research
- Issue special career development awards and training announcements to increase the population of investigators who are capable of conducting rigorous clinical treatment research
- Enhance the science of clinical research through various mechanisms, including the encouragement of innovative research designs, high-impact studies, and the development of large trial networks and core resources
- Partner with other agencies to facilitate the development and optimization of treatments, including the Food and Drug Administration and CMHS

Improving the Operation, Efficiency, and Productivity of Clinical Trials

- Work with potential grantees as they develop their research applications
- Require that applicants address a number of design, site, diversity, and coordination center issues in their applications
- Work to ensure that the overall competence and expertise of investigators to conduct proposed clinical trials as well as the operational capability of proposed projects are considered in evaluating and scoring an application
- Fund projects with demonstrated feasibility of accomplishing the proposed work
- Fund studies that address public health priority areas and demonstrate scientific importance
- Consider the use of cooperative agreements and contracts for the conduct of large-scale trials

In conclusion, Dr. Lieberman noted that it is essential that NIMH be proactive in communicating with the scientific community about research priorities and in working collaboratively with academia, the pharmaceutical industry, policymakers, service providers, and consumers.

Discussion

After thanking Dr. Lieberman for an excellent summary, Dr. Insel expressed concern about the described deficiencies in many studies with respect to subject enrollment and, in particular, that of minority participants.

Dr. Folkman commented that the recommendation regarding innovative research designs, including hybrids, should incorporate exciting developments in trial designs (e.g., preference trials). Since many members of review committees may not be familiar with these advances in research design, NIMH might promote their use by advocating specific, applicable formats in RFAs or other NIMH policy statements. Dr. Insel agreed that this is an option.

Dr. Folkman, continuing her comments on the report's recommendations for more interdisciplinary research, improvements in subject recruitment efforts, and adherence to treatment protocols, suggested that RFAs for large-scale, multicenter trials require the inclusion of personnel with sufficient skills and training to facilitate subject enrollment and participation. Additionally, more attention needs to be given to barriers that inhibit enrollment of minority group members. If studies of this issue have not been conducted as they have for AIDS research, they should be undertaken and the findings applied.

Dr. Essock suggested that an investigator's sponsoring institution be held accountable as well in devising strategies to alleviate the burdens often experienced by individual investigators around subject recruitment. She noted that periodic reviews of grant accomplishments offer an opportunity to identify sponsoring institutions that are delivering less than what was promised.

Dr. Gunnar interjected that subject recruitment problems are not restricted to clinical trials but found throughout NIMH and NIH. She suggested that perhaps some of the indirect costs awarded to sponsoring institutions might be used for establishing special offices to facilitate diversity in the human research that occurs under their auspices, including, for example, staff translators who can quickly translate study interviews or consent documents. She stressed the shared responsibility of the applicant institution with investigators in meeting recruitment goals.

Dr. Squire suggested that the Workgroup's report would be more compelling if it clarified what important clinical questions are being asked in the current trials, which funded studies (or examples) address those issues, and what they are accomplishing. A convincing, real-world rationale for treatment research could enhance the report by offering examples of the practical, relevant answers that recently completed clinical trials have obtained and how those findings can be translated immediately into practice.

Dr. Wagner remarked that the ongoing challenge will be to have mechanisms in place to ensure that future treatment research portfolios reflect pressing mental health needs across the lifespan and that new and funded treatments are applicable in a variety of settings.

Dr. Reynolds expressed concern about the limited number of K awards that provide support to investigators who are committed to treatment research. This is not sufficient, he said, to grow

the field and underscores the need for NIMH to invest more research training resources in treatment research career development. He echoed Dr. Wagner's concern for DSIR's research portfolio to reflect appropriate investments across the life cycle. He reminded the audience of one of the conclusions from last year's Council report that NIMH is not adequately investing in geriatric mental health treatment research in relation to the public health burden of mental illness in old age (see http://www.nimh.nih.gov/council/agingreport.cfm).

Ms. Hellander expressed concern that the Workgroup's report lacks a sufficiently strong statement on children considering that all adults with mental illness were once children. Parents now understand that these disorders are biological and highly heritable, and they are searching first for effective pharmacological treatments with few side effects to provide rapid relief for their children and then for proven psychosocial interventions. She pointed out that children's suffering and the irretrievable loss of time when they are too impaired to attend school and miss out on normal developmental milestones are tremendous burdens associated with mental illnesses. She suggested that any research on cost-effective interventions must take into account the time a child loses to illness while he/she waits for a treatment to take effect as well as a caregiver's lost wages.

Dr. Gary remarked that the report's attention to involving "stakeholders" did not clearly define the term. In her mind, stakeholders are universities, researchers, and the public mental health facilities located in a variety of communities that may not fully understand the concept of research or the NIMH mission. These communities as well as ethnic minority groups need to become active stakeholders in research. If a majority of funded researchers do not meet their target goals for subject enrollment, the science is severely compromised and study outcomes likely are not applicable to ethnic minority populations. To remedy this situation, researchers must become more culturally competent and more psychologically comfortable in working with ethnic minority groups. Too few principal investigators are members of minority groups or know how to reach out to these populations. These issues need to the discussed within communities of minority group members if the entire research process is not to be compromised.

Dr. Insel recalled that identifying appropriate stakeholders to be active partners in these kinds of clinical trials has been a recurrent theme in prior Council reports and at past Council meetings and that it is critical that the issue be addressed in the report under discussion.

Dr. Aguilar-Gaxiola expressed enthusiasm about the report but asked for a discussion of the data pertaining to patients enrolled in the FY 2003 adult treatment trials portfolio by race and ethnic status. He suggested that similar data be added to convey trends in the enrollment statistics over the past several years. One obvious conclusion, he noted, is that the percentage of Hispanic subjects who participated in the adult clinical trials does not reflect the growing proportion of Hispanics across the Nation. Data showing the percentage of studies achieving subject recruitment goals for minority populations should be added to the report to illustrate this important point. In addition, as the supplement to the recent Surgeon General's report on mental health concluded, mental illness causes a disproportionate burden for minority populations, including economic hardship and lost productivity. Any evaluation of treatment effectiveness must clarify the measures used in determining outcomes—that is, does effectiveness imply only a reduction or elimination of symptoms or does it also include functional issues that are at the

heart of the burden of illness.

Dr. Lieberman responded that illness burden is central to the Workgroup's recommendations regarding innovative research designs that extend beyond traditional examinations of efficacy/safety to investigate not only symptom reduction but also functional outcomes such as recovery, employability, or not being placed on disability. With respect to Hispanic representation, one barrier to enrolling sufficient numbers of Spanish-speaking subjects has been the lack of available resources to translate study instruments in a timely manner. This has not been an impediment to recruiting members of other minority groups whose primary language is English.

Dr. Tsuang suggested that the documented problems pertaining to subject recruitment, retention, and ethnic diversity might be resolved by using a naturalistic, population-based catchment area research design similar to that employed in the famous Framingham studies. While this is an expensive approach, it involves a specific ethnic group in one location that can relatively easily be followed for a long period of time. In contrast to small, single site studies, a naturalistic study with a good epidemiological sample offers the opportunity to observe interactions of patients with their families and the community and to conduct long-term follow-up.

Ms. Henry, after thanking Dr. Lieberman for his leadership, remarked that the challenge for the Council after hearing this report and the previous one on the basic science portfolio is in defining the next steps to address the weaknesses and strengths outlined in the reports. For example, the large-scale clinical trials are winding down with the completion of TADS in the near future and CATIE shortly thereafter. Should these large clinical trials be converted into effectiveness studies? With respect to the issues surrounding recruitment of minority subjects, the bigger picture needs further exploration. In addition to working with institutions that are invested in academic research, a small working group might consider potential resolutions with the Institute's Office for Special Populations. Some movement toward closer relationships with stakeholders is already underway. Through a SAMHSA initiative, public mental health directors and mental health commissioners across the country, as well as staff from CMHS and SAMHSA, are helping to inform the NIMH research agenda.

Deferred Acceptance of the Report

Rather than voting on the Workgroup's draft report, Dr. Insel suggested that the vote be deferred pending report revisions to reflect the day's discussion. In the meantime, Dr. Insel said, the report's preliminary recommendations can be instrumental in defining where the Institute needs to move in the conduct of clinical trials.

TRANSLATIONAL SCIENCE: REORGANIZING NIMH'S EXTRAMURAL DIVISIONS

Dr. Insel began his presentation by noting that the Institute's current organizational structure has facilitated excellent science; however, as noted in several Council reports, gaps remain in the research portfolio. In keeping with the Institute's public health mission to reduce the burden of mental illness and behavioral disorders through research on mind, brain, and behavior, staff

members have been discussing what research discoveries would likely transform mental health care in America. Four target areas have been identified for reducing the burden through discovery: (1) pathophysiology—to discover diagnostic tests for mental disorders, biomarkers, and new targets for treatment; (2) etiology and prevention—to explain the risk architecture of mental disorders, define genetic susceptibility, tease out the contribution of environmental factors, and ascertain prevention opportunities; (3) treatment development; and (4) new strategies for disseminating information on evidence-based treatments. The scientific accomplishments of the past decade have been enormous, and the challenge is to use the tools and knowledge in a way that can have the greatest impact on the public's mental health.

At present, three major research arms of NIMH deploy over a billion dollars in research monies: the Division of Neuroscience and Basic Behavioral Science (DNBBS), the Division of Mental Disorders, Behavioral Research and AIDS (DMDBA), and the Division of Services and Intervention Research (DSIR). Additionally, the Division of Intramural Research Programs (DIRP) provides an in-house capacity for rapidly addressing research opportunities, and the Division of Extramural Activities (DEA) provides leadership in developing extramural programs and policies, peer review of grant and contract applications, and grant management support.

In a restructured NIMH model, which would increase the major research divisions from three to five, a vigorous and successful basic (bench) science division would be retained at the discovery end of the continuum, with a strong clinical trials and services research division on the opposite (practice) side of the effort. Between the two would be separate translational research programs for adults and for children, with a separate division encompassing programs on health and behavior, AIDS, and other projects that focus on treatment adherence, risk assessment, and the application of basic cognitive and behavioral science to health problems. The guiding philosophy will be to advance research concepts and investigators along the continuum and across organizational structures from basic science to practice that ultimately makes an impact on practice.

Dr. Insel offered three ways to facilitate translational research at NIMH:

1. Develop proactive program teams with an assigned, specific public health-related focus such as identifying a biomarker for bipolar disorder, developing a treatment for the cognitive symptoms of schizophrenia, or discovering autism's genetic risk architecture. It is critical that these team have the resources to address major needs. The MATRICS and Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) projects are models of such multi-disciplinary involvement.
2. Provide incentives for encouraging co-funding, handoffs, and teamwork across organizational boundaries.
3. Develop the intellectual life of the NIMH community to ensure that staff members are exposed not only to the best ideas that are emerging from within the Institute but also to exciting discoveries at other NIH Institutes.

As an example of how a refocused organizational structure at NIMH could pave the way for speeding the translation of a scientific discovery into a practical application,
Dr. Insel referenced a report in the April 29 issue of the *New England Journal of Medicine* (see

Lossos, I., Czerwinski, D., Alizadeh, A., Wechser, M., Tibshirani, R., Botstein, D., and Levy, R. "Prediction of Survival in Diffuse Large-B-Cell Lymphoma Based on the Expression of Six Genes"). The investigators studied 36 genes whose expression had been reported to predict survival in diffuse B-cell lymphoma and discovered through microarrays that a whole group of genes were either up- or down-regulated when tumors were removed. Moreover, the microarray pattern of the treatment resistant tumors differed from that of the treatment responsive ones. After the microarray data were converted to a high-throughput PCR format that could be analyzed quickly in most laboratories, these investigators conducted a large-scale clinical trial, which verified that a panel of six key genes could predict with almost 100 percent accuracy the patients who would and would not respond to treatment.

While the science of mental disorders is not yet at this stage, such practically applicable discoveries may not be far away. In fact, studies of the serotonin transporter gene (SERT LPR) may soon yield equally exciting results with respect to depression treatment. This transporter has 27 different variations, but one particular genetic variation in the promoter region—which has either a long or short version—seems to be key. A meta-analysis of its effects that was published in 2002 found that homozygous persons with the long version of the transporter were more likely than those with the short version to respond to depression treatment with a selective serotonin reuptake inhibitor (SSRI) (see Serretti, A., Lilli, R., and Smeraldi, E. "Pharmacogenetics in Affective Disorders." *European Journal of Pharmacology* 438(3):117-28, 2002. Review). Subjects with the short version of the designated transporter also were more likely to have severe adverse side effects from treatment with an SSRI (see Perlis, R.H., Mischoulon, D., Smoller, J.W., Wan, Y.J., Lamon-Fava, S., Lin, K.M., Rosenbaum, J.F., and Fava, M. "Serotonin Transporter Polymorphisms and Adverse Effects with Fluoxetine Treatment." *Biological Psychiatry* 1;54(9):879-83, 2003). While this is only one gene, intensive studies over the next few years of a panel of eight or nine similar genes might reasonably lead to capabilities for predicting individual responses to particular treatment with SSRIs and who would likely be vulnerable to dangerous side effects.

Opportunities also abound for using neuroimaging techniques to achieve similar breakthroughs. Dr. Helen Mayberg at Emory University has identified a brain region—Area 25—that appears to be very responsive in persons who either receive SSRI treatment or participate in cognitive behavioral therapy (CBT) for major depressive disorder. Although this brain region is still on the frontier of research, clinical studies suggest that it may be key to understanding the pathology of depression. More basic science studies are needed that focus on the biochemical composition of Area 25, the subgenual part of the anterior cingulate, its projections and connectivity, and how it develops in the early years. It also is important to ascertain whether, as Dr. Mayberg is asking, the activity changes in this region that apparently happen within the first few days following initiation of SSRI treatment or CBT can be used as accurate, quick predictors of a positive treatment response. This would be crucial information since a clinical response to these treatments may take 6 weeks or longer. The ultimate goal is to develop personalized interventions based on a solid research foundation for predicting treatment response.

In conclusion, Dr. Insel reported that plans for the reorganization should be finalized over the summer and described in more detail at the September Council meeting. By October, a new structure should be in place. He reassured the constituent community that the reorganization will

not eliminate particular research areas; rather, the goal is to maximize the opportunities for new discoveries and aid the Institute in fulfilling its mission and mandate from Congress.

Discussion

Dr. Salovey applauded the new emphasis on translation that will capitalize on significant scientific opportunities in the field of mental health while keeping the strong pillars of basic and applied science in place. As the priority-setting processes conclude, however, staff work will become even more critical to reshaping the kinds of research that NIMH-supported investigators conduct. He urged Dr. Insel to give careful attention to hiring people from multiple disciplines to fill new roles and replace departing employees so that the tradition of high-quality and knowledgeable staff work continues. Dr. Insel replied that recruitment efforts are directed at finding the brightest and best applicants.

Dr. Tsuang, after congratulating Dr. Insel on the clear rationale he offered for the proposed reorganization and commending the recommendations made by the two Council workgroups that reviewed the basic science and clinical trials portfolios, asked whether an equivalent effort should be made to review the genetics portfolio that is so important to an examination of biomarkers and gene expression. Dr. Insel requested that the discussion be tabled for a future meeting because the field is moving so quickly. The anticipated completion of NIH's Haplotype Map Project within the next 6 months, which will catalog human genetic variations of most importance to health and disease, may dramatically change future research directions.

Dr. Kalin, remarking that this may be a watershed Council meeting from the standpoint of clinical trials and basic neuroscience as well as organizational changes, suggested that the definition of high-risk research be changed so that translational projects, often considered high risk in the past, become mainstream efforts.

Dr. Insel commented on the importance on informing the public and scientific community about the reorganization. Once it is satisfactorily underway, the new NIMH structure will be described on the NIMH Web site (see http://www.nimh.nih.gov/).

Mr. McNulty expressed his appreciation for the important information presented by the workgroups and the conceptual model for reorganizing NIMH that Dr. Insel provided and stressed the need to involve all stakeholders, including advocacy group members and other consumers, in the plans to develop the intellectual life of the mental health community. Too often information dissemination only entails journal publications for the scientific community and adding documents to the Web site. He suggested that this is an opportune time for NIMH to be more proactive in reaching out to educate the public and in the process, address those who question the existence of mental illness and the value of treatment.

Ms. Hellander commended the reorganization plan and the centerpiece focus on translational research directed at children.

CONCEPT CLEARANCE

Dr. Steven Moldin, Director, Office of Human Genetics and Genomic Resources, DNBBS, presented a concept for clearance that pertains to "Identifying Genes that Confer Susceptibility to Autism." As background, he explained that autism is one of the complex disorders within the NIMH purview in which both genes and environment play important roles. While the way in which genes actually produce the phenotype (disease) is unclear, it seems likely that multiple genes, each with a small effect, interact with each other to contribute to susceptibility. The key implication is that very large datasets are essential to identifying the multiple genes involved.

Some recent advances in the field of autism genetics are promising. Namely, several genomic regions and particular genes have been identified as candidates, although none have unequivocally been implicated as one of the actual genes or mutations in those genes. Another helpful development is the availability in the public domain of several very large datasets—one maintained by NIMH and another by Cure Autism Now (CAN) that contains resources collected from affected individuals and their family members. The National Alliance of Autism Research (NAAR) also has organized a large, collaborative, worldwide genome project that has assembled over 1,300 families reflecting 3,000 autism-affected individuals with whom ongoing genome scans are being conducted. Additionally, the NIMH Autism Genetics Repository Initiative (AGRE) will have, by the end of 2004, information on over 1,600 families and many other unrelated affected individuals that can be used in other genetic studies.

The proposed RFA—with the possibility of a later Program Announcement—will focus on several key research areas: identifying positional candidate approaches to find disease genes; conducting association analyses and other genetic studies including linkage disequilibrium mapping genetic studies; gene/environment interactions; epigenetic mechanisms—the complex molecular mechanisms involving gene action that have not been studied in traditional studies; initiating functional studies to discover how these genes act to cause disease susceptibility; and ascertaining some of the shared mechanisms of autism and Fragile X syndrome—another disorder where the molecular mechanism or the involved genes/proteins have been identified and are being studied. The observation that some children have both autism and Fragile X syndrome introduces the concept that there are shared etiologic mechanisms or genetic factors. NIMH will host a workshop in July for experts from both fields to discuss how best to proceed with identifying and elucidating the shared genetic mechanisms.

The goal of the proposed RFA is to identify specific disease genes that produce susceptibility to autism by using state-of-the art molecular genetics and preexisting datasets. The objective is to ensure a broad sharing of responsibility with the scientific community through a multi-national, multi-source effort that offers ample funding for identifying these genes in a short period of time and ascertaining how they cause disease susceptibility.

Discussion

Dr. Insel commented that the proposed RFA reflects the shift at NIMH and within NIH to a broad sharing across the scientific community and public/private partnerships that may include many advocacy groups. Additionally, the proposed project exemplifies a new thrust away from

searches for linkages and gene discovery to looking for the molecular lesion.

To a question from Dr. Tsuang regarding whether the RFA entails working with the already collected 1,200 pedigrees or collecting more of them, Dr. Moldin explained that the major focus would be analyses of the existing datasets, which include the NIMH repository, CAN resources, and the Autism Genome Project that NAAR is supporting. However, as more funds become available from other sources, other populations could be added that are not now represented in these datasets. Specifically, almost all the samples collected to date are from Caucasian populations with few Hispanics or Asians. Dr. Tsuang clarified that, if linkage and sib pairs are not the primary focus of the data collection and analyses, a different strategy may be needed to focus on the association rather then the traditional linkage.

Approval of the Concept

Following this discussion, Dr. Insel requested and received a motion to approve the concept. This was seconded and unanimously accepted by voice vote without further discussion.

PUBLIC COMMENT

The public comment period opened with Ms. Alison Kutchma, a member of the Child and Adolescent Bipolar Foundation (CABF), commending the help she received from this organization as a mother of three children who suffer from bipolar disorder. The CABF was founded in 1999 by parents of bipolar-diagnosed children who found it impossible to attend face-to-face support groups offered by mental health organizations. As an alternative, they established a Web site that has become a 24-hour virtual community for more than 20,000 affected families and a source of science-based information about diagnosis and treatment resources for bipolar disorder for nearly 50,000 unique Internet users each month. This CABF Website, Ms. Kutchma continued, not only informed her about the illness that was devastating her family and robbing her offspring of carefree childhoods but also offered great comfort and renewed hope as she shared her troubles with others, learned about effective treatments, and finally found an excellent physician, who diagnosed her children and now follows them in a special study. Despite her own good fortune in finding the CABF Web site early in her own family's long sojourn, Ms. Kutchma reflected that too many children still suffer from a life-threatening and treatable medical condition while their parents believe they are responsible for their offspring's behavioral problems. She pleaded for more research on the effects of early diagnosis and treatment as well as more support for cost-effective Internet-based outreach services and education that can save families and lives.

Dr. Insel noted that NIMH's intramural program focuses on particularly urgent public health issues—of which pediatric bipolar disorder is one in which Dr. Ellen Leibenluft is conducting some remarkable research.

Dr. Steven Breckler, Executive Director for Science at the American Psychological Association (APA), commended the Basic Science Workgroup's diligence and reported APA's gratification with the composition of the panel–about which APA was initially consulted. In urging Council and NIMH to take the Workgroup's recommendations seriously, particularly the relevance of

behavioral science to the Institute's mission, Dr. Breckler made three points:

1. The Workgroup clearly concluded that basic behavioral research is essential to NIMH's mission and should principally focus on dimensions of individual and group behavior that advance knowledge about which individuals are more resilient—or vulnerable—to mental and behavioral disorders and how social and environmental factors impact the development, diagnosis, prevention, and treatment of mental illness.
2. The emphasis given, in both the Workgroup's report and the reorganization plans, to integrating the sciences and conducting more translational research is cause for some concern. While interdisciplinary research is undoubtedly important and supported by the APA for bridging the gap between research and practice, basic science that does not focus on translation is still needed. However, it is impossible to conduct interdisciplinary research without the disciplines to draw from or to perform translations without material to translate. Further, the interest in integrating basic behavioral sciences with neuroscience seems to be a one-way street in which neuroscience informs behavioral science. Actually, basic behavioral science has much to offer research on the biological, cellular, and genetic aspects of neuroscience. Indeed, neuroscience will not necessarily advance an understanding of mental health/illness unless it is informed by the problems basic behavioral science has identified.
3. While the proposed changes may resolve a short-term budgetary problem, careful consideration should be given to the long-term consequences of such a significant reorganization and, for example, the types of new training programs that must be created to foster and nurture an interdisciplinary research community. It seems critical that basic behavioral research has a continued, visible presence after the NIMH reorganization is complete, including relevant scientific expertise on the NIMH staff. To retain and develop the intellectual life of the NIMH community—as well as follow the Workgroup's advice—continued research on emotion, social interactions and relationships, and stereotyping and prejudice is needed. Because NIMH has already lost key staff in those very areas, it is difficult to imagine how the Institute can move forward as proposed without replacing this lost scientific expertise with all due speed.

Dr. Insel said that he welcomed the opportunity to continue to work with APA to publicize the proposed changes at NIMH and to clarify future research directions.

Dr. Debbie Franko, representing the Academy for Eating Disorders, appreciated the attention given to the clinical trials portfolio but expressed concern that anorexia nervosa was grouped in the "other" category since it is a lethal psychiatric disorder. Although an RFA was recently issued that offers the promise of new treatments, little is known about risk or prevention or about eating disorders among ethnic minority women. The best treatment for bulimia nervosa helps only 35 to 40 percent of women with this diagnosis, which has incredibly harsh consequences. While great attention is currently given to obesity and its prevention, the inadvertent impact of this campaign may be to get young people thinking more about diets and body images that increase their risk for eating disorders. In response, Dr. Insel noted that the recent RFA pertaining to anorexia nervosa generated many grant applications that are in the review phase and will be considered at the next Council session.

Ms. Cynthia Folcarelli, Executive Vice President of the National Mental Health Association (NMHA), also commended the two Workgroup reports, saying that NMHA agrees with most of the conclusions and looks forward to working with NIMH toward implementation but also expressed several concerns. The emphasis given to research on resilience, prevention, and mental health promotion seemed inadequate. Also, the recommendation to make research on normal human development the purview of other Institutes raised a red flag since knowing how to maintain mental health seems to be as important as learning what causes illness. In addition, too little attention seemed to be given to cultural competence research—not just enrolling diverse populations in clinical trials but investigating effective outreach strategies and interventions for different populations. Finally, there seemed to be some confusion about whether SAMSHA or NIMH is responsible for services research [*note: In 1992,Congress passed the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) Reorganization Act (P.L. 102-321), abolishing ADAMHA. The Act specified that the research components (including services research) of NIAAA, NIDA, and NIMH would be retained at the Institutes, which rejoined NIH*.] Since the success of the modified portfolio appears to hinge on the definition of mental illness, NMHA urges that this be defined as broadly as possible—to include not only diagnosable mental illnesses but also symptoms and behaviors that affect functioning and well-being. This is particularly critical for children who are difficult to diagnose and already underrepresented as a research focus. The current controversy over using antidepressant medications for children demonstrates the lack of adequate tools for families or clinicians to distinguish children with clinical depression—which may require one set of interventions—from children with symptoms of depression that do not meet clinical criteria but still warrant some form of intervention.

Ms. Blanca Fuertes, an employee of the Office of Rural Health Policy (ORHP) in the Health Resources and Services Administration, asked whether the report from the Clinical Trials Workgroup used any data on urban versus rural tracks. A forthcoming report to HHS Secretary Thompson from the National Advisory Committee on Rural Health and Human Services has a chapter on mental health that addresses several relevant concerns, including the lack of rural populations' representation in clinical trials. One quarter of the U.S. population lives in rural communities and 80 percent of the land is considered rural. Although resource scarcity and geographic barriers are daunting, rural communities should be represented in the NIMH clinical trials. Since she has been assigned to manage ORHP's mental health portfolio, Ms. Fuertes, offered her services in this effort. In response, Dr. Insel welcomed the assistance offered by Ms. Fuertes and noted that the President's New Freedom Commission report has a similar section on rural mental health needs.

Dr. Joan Levy Zlotnik, Executive Director of the Institute for the Advancement of Social Work Research (IASWR), commented that the report from the Clinical Trials Workgroup raised important issues about the significance and complexity of interventions research and pointed up the need for more collaboration between researchers and consumers/practitioners to ensure that funded studies address critical problems of research design, protocol adherence, and enrollment. The IASWR looks forward, as an organization of social workers who provide the majority of mental health services in this country, to working with Council and NIMH on these issues.

Dr. Darrel Regier, Director of Research at the American Psychiatric Association (APA) and Director of the American Psychiatric Institute for Research and Education, opined that this

Council meeting was a watershed event, particularly the neuroscience portfolio review that examined NIH commitments to this field across 14 Institutes. Although NIMH was, originally, the only source of support for basic neuroscience and behavioral science, the past 50 years have witnessed the spread of funding for both these areas across the whole of NIH. Hence, it may be useful to conduct a similar examination of responsibilities for behavioral science across all the NIH Institutes so that NIMH can coordinate its efforts with other Institutes. The APA also is looking closely at how genetics and epidemiology will be linked both to the basic neuroscience issues and to services research and prevention questions. Clarification of these strategies as NIMH goes forward with its reorganization will be extremely important. The APA remains committed to translating research into services as evidenced by the research track organized by NIDA at the last annual meeting where participants represented the major neurosciences, behavioral sciences, and a wide array of clinical science researchers. The APA welcomes NIMH's development of a research track for the next meeting on communicating the promise of science to new practitioners. APA also has launched an effort to translate research into diagnosis, using an NIH conference grant to review all of the science that underlies diagnosis. Major attention will be given to international, cross-cultural, geographical, and gender representation. Gender and geriatrics workgroups are currently looking at the research and evidence basis of those areas for the next DSM-V and a congruent international classification of diseases. The APA is also looking forward to working with the NIH Roadmap group and with its practice research network to engage practitioners in contributing to an evidence base for clinical practices.

Dr. Insel replied that Dr. Zerhouni has asked the Advisory Council to the Director to conduct a NIH-wide review of behavioral science under the direction of Dr. Linda Waite. Following a recent initial meeting, this group expects to portray the topography of behavioral sciences throughout NIH over the next few months and recommend future directions.

ADJOURNMENT

After reminding members that Council will reconvene on Monday and Tuesday, September 20-21, 2004, Dr. Insel adjourned the 206th meeting of the NAMHC at 1:00 p.m. on May 14, 2004.

I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.

_____

Thomas R. Insel, M.D., Chairperson